Increased non-stationarity of heart rate during general anaesthesia with sevoflurane or desflurane in children

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Background. During general anaesthesia, the most prominent change in heart rate variability (HRV) is a decrease in the magnitude of heart rate (HR) oscillation in the high- and low-frequency ranges. In children receiving sevoflurane or desflurane, we observed a significant increase in HR non-stationarity, that is, a significant change of mean HR over time. The aim of our study was to describe this increased non-stationarity and compare it with the decrease in the magnitude of HR oscillation.

Methods. Sixty children received sevoflurane (n=30) or desflurane anaesthesia (n=30). The magnitude of HR oscillation and non-stationarity during pre-anaesthesia and anaesthesia were measured by spectral and Hurst analyses using structure function, respectively.

Results. Low- and high-frequency powers decreased significantly and the very-short-term (2≤τ≤8 s, Hα) and short-term Hurst exponent (8≤τ≤45 s, Hb) increased significantly during the anaesthetic period compared with the pre-anaesthetic period, regardless of the anaesthetic agent [sevoflurane: mean (SD) Hα 0.414 (0.169) vs 0.252 (0.0655), Hb 0.481 (0.169) vs 0.078 (0.0409); desflurane Hα 0.336 (0.171) vs 0.261 (0.0614), Hb 0.471 (0.221) vs 0.0813 (0.049)]. Stepwise discriminant analysis showed that the short-term Hurst exponent was better than the spectral indices at differentiating between the pre-anaesthetic period and anaesthetic period.

Conclusions. During sevoflurane and desflurane anaesthesia in children, there is a significant increase in very-short-term and short-term HR non-stationarity. Furthermore, the greater short-term non-stationarity differentiates better between the pre-anaesthesia and anaesthesia than the decreased magnitude of HR oscillation in the high- and low-frequency ranges.

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Characterization of heart rate variability (HRV) is valuable in children and in adults for assessing alterations in heart rate (HR) regulation mechanisms, including autonomic modulation, and for predicting short- and long-term disease outcomes.1–6 Likewise, characterization of HRV during general anaesthesia in children may be useful in the investigation of the influence of anaesthetic agents cardiovascular regulation,7–11 and in evaluating or predicting the anaesthetic or post-anaesthetic outcomes such as anaesthetic depth,12–14 recovery time, and the magnitude of unstable fluctuations in systemic arterial pressure and HR.15–18

During general anaesthesia, the most frequently used method of HRV characterization is quantification of frequency-domain oscillation using spectral analysis of the HR. Low-frequency (0.04–0.15 Hz) and high-frequency (0.15–0.4 Hz) oscillations are markedly suppressed19 20 so that using this method alone may be unhelpful.

We observed markedly increased non-stationarity of HR during general anaesthesia in children. Non-stationarity of HR is defined as a significant change in the mean value of HR with time, that is, a progressive bradycardia or tachycardia. Sometimes oscillation is so greatly suppressed that non-stationarity dominates the HRV. Even when
were ventilated with 8% of sevoflurane in oxygen 100%.

Another aim was to assess the value of non-stationarity in differentiating between the pre-anaesthetic and anaesthetic states.

In order to evaluate the oscillatory and non-stationarity behaviour of HR, we performed power spectral analysis and Hurst analysis using the structure function of HR. This form of Hurst analysis has an inherent advantage for calculation of non-stationarity, unlike the other Hurst analysis methods such as rescaled range analysis, scaled windowed variance, and disperval analysis.

**Methods**

This study was approved by the Committee of Clinical Investigation of our institution. Sixty children undergoing elective orthopaedic surgery, ASA physical status I and II, aged 2–8 yr were enrolled in the study (Table 1). Thirty were given general anaesthesia with sevoflurane and the other 30 received desflurane. Informed consent was obtained from the parents. Patients with cardiovascular abnormalities, developmental delays, seizures, and metabolic or pulmonary diseases were excluded.

The day before surgery, all children visited the monitoring room, and the ECG was recorded in the pre-anaesthetic state for 20 min. This room is beside the operating room, and the ECG was recorded in the pre-anaesthetic period when the ECG data were recorded during anaesthesia. No surgical intervention was performed during the recording of ECG and no opiates were administered.

| Table 1 Patient characteristics. Values are number of patients, mean (range) or mean (SD) |
|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| M/F                               | 14/16                             | 17/13                             |                                  |                                  |
| Age (yr)                          | 7.0 (1–14)                        | 7.6 (0.8–15)                      |                                  |                                  |
| Body weight (kg)                  | 28.3 (13.4)                       | 29.1 (15.1)                       |                                  |                                  |
| Height (cm)                       | 118.4 (34.0)                      | 122.9 (30.4)                      |                                  |                                  |
| Haemodynamic variables            |                                  |                                  |                                  |                                  |
| Systolic arterial pressure (mm Hg)|                                   |                                   |                                  |                                  |
|                                  | 105.7 (11.6)                      | 111.8 (20.9)                      | 106.4 (12.7)                     | 115.3 (20.2)                     |
| Diastolic arterial pressure (mm Hg)|                                   |                                   |                                  |                                  |
|                                  | 56.9 (8.6)                        | 55.0 (11.5)                       | 57.9 (9.9)                       | 55.0 (9.4)                       |
| Heart rate (beats min⁻¹)          |                                   |                                   |                                  |                                  |
|                                  | 96.7 (9.6)                        | 100.8 (25.8)                      | 100.0 (9.7)                      | 109.4 (23.1)                     |

**Data pre-processing**

All ECG data were reviewed by visual inspection. Segments were discarded in cases of signal loss, significant noise, and the presence of atrial or ventricular extrasystoles. The R peak was determined by the algorithm described by Pan and Tompkins.

RR intervals (RRI) were measured and tested for the presence of outliers (HR < 30 or > 200 beats min⁻¹). Any outliers were removed. All RRI data were linearly interpolated at 1000 Hz to construct a real-time series of RRIs, and then re-sampled at 2 Hz. The 1800 points (15 min of data) were used for calculating HRV indices. All data processing, including visual inspection, spectral analysis, and Hurst analysis, was conducted using Matlab 7.0.1 (Mathwork Inc., MA, USA).

**Power spectral analysis**

Power spectral analysis was by a fast Fourier transformation. The RR interval data were divided into 512 data point sections (4.26 min of data). After being detrended, these sections were fast Fourier transformed and averaged to form a power spectral density function. We calculated total power (TP), very-low-frequency power (VLFP), low-frequency power (LFP), and high-frequency power (HFP).
by integrating the power spectral density curve in the 0–0.4, 0–0.04, 0.04–0.15, and 0.15–0.4 Hz ranges, respectively. Normalized LFP (nLFP) and normalized HFP (nHFP) were then calculated by the following formula: 29

$$nLFP(\%) = \frac{LFP}{LFP(pre-anaesthetic) + HFP(pre-anaesthetic)} \times 100,$$

$$nHFP(\%) = \frac{HFP}{LFP(pre-anaesthetic) + HFP(pre-anaesthetic)} \times 100.$$

**Hurst analysis using structure function** 21 22 30

The nRRI was denoted as RRI (t) and we calculated the fluctuations in the difference as the structure function of RRI $\Delta y_t(t) = |RRI(t + \tau) - RRI(t)|$ for different time increments, $\tau$ s. $\Delta y_t(t)$ is the magnitude of the change in RRI after $\tau$ s. In order to perform Hurst analysis, this study estimated the average of these local variations, which depended on the scaled time increments shown in the following equation:

$$< \Delta y_t(t) > \sim \tau^H$$

where $<$ indicates the time average and $\sim$ indicates the presence of the power law behaviour of $< \Delta y_t(t) >$ against $\tau$

$$H = \lim_{\tau \to 0} \frac{< \Delta y_t(t) >}{\tau}.$$

In order to quantify the scaling behaviour of $< \Delta y_t(t) >$, this value was plotted for $\log_2 (\tau) = 2 \ldots 10$. The scaling region was then obtained and the slopes of $< \Delta y_t(t) >$ were calculated against $\tau$ at the scaling region, thus yielding the Hurst exponent, $H$.

When the values of $\log_2 < \Delta y_t(t) >$ vs $\log_2 \tau$ were plotted, two linear scaling relations could be observed approximately at $2 \leq \tau \leq 8$ and $8 \leq \tau \leq 45$ s. Therefore, very-short-term and short-term generalized Hurst exponents ($H_a$, $2 \leq \tau \leq 8$, and $H_b$, $8 \leq \tau \leq 45$ s, respectively) could be obtained from equation (1). The very-short-term Hurst exponent was defined as $H_a$ and the short-term Hurst exponent was defined as $H_b$. Since $H$ is the slope of $< \Delta y_t(t) >$ against $\tau$ in the log-log scale and $H>0$, this value measures the rate of increase in the mean RRI difference over time $\tau$. In other words, the exponent measures how greatly the mean RRI changes as time advances. Accordingly, unlike the other methods of Hurst analysis, this measurement is well suited for measuring non-stationarity.

**Statistical methods**

Repeated-measures ANOVA was performed to compare the differences in HRV indices during pre-anaesthetic and anaesthetic periods. $P$-values $<0.05$ were considered significant. All values shown are mean (SD). To find the best discriminator among all of the variables between the pre-anaesthetic and anaesthetic states, we used stepwise discriminant analysis. The variable that produces the largest $F$ value is the best discriminating variable selected, provided $F$ is statistically significant. All statistical analyses were conducted using SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

**Results**

Haemodynamic variables are shown in Table 1. HRV indices and comparisons between the indices during the pre-anaesthetic period and the anaesthetic period are presented in Table 2. Comparisons between those of the sevoflurane group and those of the desflurane group during the pre-anaesthetic and anaesthetic period are also presented in Table 2.

During sevoflurane anaesthesia, the mean and standard deviation of RRI did not change significantly. The TP, LFP, HFP, nLFP, and nHFP significantly decreased when compared with the pre-anaesthetic period (Table 2). During desflurane anaesthesia, mean, standard deviation, TP, LFP, HFP, nLFP, and nHFP decreased significantly when compared with the pre-anaesthetic values. $H_a$, $H_b$, and $H_b/H_a$ were significantly greater during sevoflurane and desflurane anaesthesia than during the pre-anaesthetic period. The values of TP, LFP, HFP, and nHFP of RRI during desflurane anaesthesia were significantly lower than those during the period of sevoflurane anaesthesia. However, all Hurst indices during the desflurane anaesthesia were not significantly different to those during sevoflurane anaesthesia. Stepwise discriminant analysis showed that the short-term Hurst exponent, $H_b$, was best at differentiating between pre-anaesthetic and anaesthetic states for both sevoflurane ($F$ value: 15.5, $P=0.001$, Table 2) and desflurane ($F$ value: 65.9, $P=0.000$, Table 2).

Figure 1A and B displays HR tachograms during the pre-anaesthetic and anaesthetic, respectively, period that were calculated from the RRI sequences in Figure 1C and D, respectively. Figure 1C and D shows two representative 15 min RRI sequences recorded before and during, respectively, desflurane anaesthesia. The most marked change in HR behaviour during desflurane anaesthesia is the decreased magnitude of oscillation, which is further corroborated by the markedly decreased low- and high-frequency powers (345.4 and 92.5 ms$^2$, respectively, in Fig. 2A, vs 1.1 and 2.0 ms$^2$, respectively, in Fig. 2B). However, another prominent difference in HR behaviour is that during anaesthesia the mean of HR changes significantly with time, that is, the HR is significantly non-stationary (Fig. 1A, arrows), which is not the case in the pre-anaesthetic state (Fig. 1A). The increased non-stationarity of very short-term and short-term scales is further confirmed by higher $H_a$ (0.2877 vs 0.4243) and markedly higher $H_b$ (0.0165 vs 0.8395).
Since $H_b$ best discriminated between anaesthetic and pre-anaesthetic periods, and $H_b$ is calculated from $D_y(t)$, we show how $D_y(t)$ and $\Delta y(t)$ differ between the pre-anaesthetic and anaesthetic states when $t$ increases from 8 to 45 s. Figure 1 displays the sequences of $D_y(t)=8s$ and $D_y(t)=45s$ calculated from the RRI sequences shown in (C) and (D), respectively. Each horizontal line in (E), (G), (F), and (H) is the time average $<\Delta y>_t$ of each of the $\Delta y$ sequences.

Since $H_b$ best discriminated between anaesthetic and pre-anaesthetic periods, and $H_b$ is calculated from $<\Delta y>_t$ ($8 \leq t \leq 45$ s), we show how $\Delta y$ and $<\Delta y>$ differ between the pre-anaesthetic and anaesthetic states when $t$ increases from 8 to 45 s. Figure 1 displays the sequences of $\Delta y_{=8s}$ and $\Delta y_{=45s}$ calculated from the RRI during the pre-anaesthetic state shown in Figure 1C. Each value of $\Delta y_{=8s}$ and $\Delta y_{=45s}$ is the magnitude of RRI

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane Pre-anaesthetic</th>
<th>Sevoflurane Anaesthetic</th>
<th>Desflurane Pre-anaesthetic</th>
<th>Desflurane Anaesthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RRI (ms)</td>
<td>625.9 (62.5)</td>
<td>632.9 (162.5)</td>
<td>619.0 (60.6)</td>
<td>573.0 (123.1)</td>
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<td>Standard deviation of RRI (ms)</td>
<td>38.5 (6.6)</td>
<td>49.1 (29.9)</td>
<td>36.1 (6.5)</td>
<td>30.5 (19.6)</td>
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<td>TP (ms$^2$)</td>
<td>1258.5 (152.7)</td>
<td>884.7 (79.8)</td>
<td>1205 (121.6)</td>
<td>447.6 (57.8)</td>
</tr>
<tr>
<td>VLFP (ms$^2$)</td>
<td>755.3 (207.6)</td>
<td>780.2 (169.5)</td>
<td>677.2 (216.9)</td>
<td>390.1 (114.3)</td>
</tr>
<tr>
<td>LFP (ms$^2$)</td>
<td>322.9 (42.8)</td>
<td>69.8 (16.3)</td>
<td>370.7 (31.8)</td>
<td>47.8 (23.8)</td>
</tr>
<tr>
<td>HFP (ms$^2$)</td>
<td>180.3 (8.1)</td>
<td>34.7 (7.5)</td>
<td>157.1 (5.9)</td>
<td>9.8 (1.2)</td>
</tr>
<tr>
<td>nLFP (%)</td>
<td>66.7 (12.6)</td>
<td>12.3 (4.5)</td>
<td>67.3 (11.9)</td>
<td>10.9 (2.8)</td>
</tr>
<tr>
<td>nHFP (%)</td>
<td>34.3 (12.6)</td>
<td>7.7 (1.3)</td>
<td>33.7 (11.9)</td>
<td>1.3 (1.0)</td>
</tr>
<tr>
<td>$H_a$</td>
<td>0.252 (0.065)</td>
<td>0.414 (0.169)</td>
<td>0.261 (0.0614)</td>
<td>0.336 (0.171)</td>
</tr>
<tr>
<td>$H_b$</td>
<td>0.078 (0.0409)</td>
<td>0.481 (0.169)</td>
<td>0.0813 (0.049)</td>
<td>0.471 (0.221)</td>
</tr>
<tr>
<td>$H_b/H_a$</td>
<td>0.319 (0.19)</td>
<td>1.178 (0.596)</td>
<td>0.326 (0.189)</td>
<td>1.125 (0.454)</td>
</tr>
</tbody>
</table>

### Fig 1

(A and B) Representative HR tachograms from a patient who received desflurane. The graphs show the pre-anaesthetic (A) and anaesthetic (B) period and were calculated from RRI sequences presented in (C) and (D), respectively. Note a marked non-stationarity of heart rate. (C and D) Two 15 min long RRI sequences from the same patient recorded before (C) and during (D) general anaesthesia. (E and G) The sequences of $D_y(t)$ of $D_y(t)=8s$ (E) and of $D_y(t)=45s$ (G) calculated from the RRI sequence shown in (C). The sequences of $D_y(t)$ of $D_y(t)=8s$ (F) and $D_y(t)=45s$ (H) calculated from the RRI sequence are shown in (D). Each horizontal line in (E), (G), (F), and (H) is the time average $<\Delta y>_t$ of each of the $\Delta y$ sequences.
change at 8 and 45 s after a given time point. The mean of $\Delta y_{t=45s}$ ($\Delta y_{t=45s} = 32.4$ ms, the horizontal line in Fig. 1e) is not significantly different from the mean of $\Delta y_{t=8s}$ ($\Delta y_{t=8s} = 32.0$ ms, the horizontal line in Fig. 1c). In other words, in the pre-anaesthetic state on average, the magnitude of change of RRI at 45 s after a certain instant does not differ from that at 8 s after the instant, which implies that the mean of the RRI is unchanged as time evolves from 8 to 45 s after the instant. Figure 1f and h displays the sequences of $\Delta y_{t=8s}$ and $\Delta y_{t=45s}$ calculated from the RRI during the anaesthetic period shown in Figure 1f. The mean of the $\Delta y_{t=45s}$ ($\Delta y_{t=45s} = 23.3$ ms, the horizontal line in Fig. 1f) is significantly larger than the mean $\Delta y_{t=8s}$ ($\Delta y_{t=8s} = 6.4$ ms, the horizontal line in Fig. 1f). In other words, during anaesthesia, the mean change in the RRI at 45 s after a given time is significantly larger than that at 8 s. This indicates a large non-stationarity with passage of time.

Though we have demonstrated only the time evolution from 8 to 45 s during anaesthesia, the change in mean RRI can be found in any short-term time period within the scale, such as that from 9 to 11 s. This is due to the fractal property of the scale invariance, that is, linear scaling behaviour, and a similar slope from 8 to 45 s (Fig. 2c and d).

**Discussion**

The major new finding of the present study was that, in children, the short-term and very-short-term Hurst exponents increased significantly during both sevoflurane and desflurane anaesthesia, compared with the pre-anaesthetic period. Another new finding was that for both sevoflurane and desflurane anaesthesia, the short-term Hurst exponent was better than other HRV indices, including spectral indices, in discriminating between pre-anaesthetic and anaesthetic periods.

This indicates that the HRV characteristic that differentiates between pre-anaesthesia and anaesthesia most effectively in children may be increased short-term non-stationarity rather than decreased low- and high-frequency oscillations. Since two different general anaesthetics both produced similar prominent changes, these changes are probably a non-specific response to general anaesthesia. Thus, we suggest that when characterizing HRV during general anaesthesia in children evaluation of short-term non-stationarity by short-term Hurst exponent and the evaluation of oscillation by spectral indices should be considered.

In the pre-anaesthetic period in the sevoflurane group and the desflurane group, the mean values of the short-term...
Hurst exponent were 0.078 and 0.081, respectively, that is, close to zero. During sevoflurane and desflurane anaesthesia, these mean values were 0.481 and 0.471, respectively, that is, close to 0.5. When the Hurst exponent value equals zero, the time series is completely anti-persistent, and when the time series increases then the Hurst exponent always decreases, and vice versa. When the Hurst exponent equals 0.5, the time series is random; when the time series increases, then an increase or decrease is equally probable. Accordingly, in the pre-anaesthetic period if HR increases at a certain time, then at 8–45 s after that time HR will usually decrease, and vice versa for initial decrease in HR. Consequently, the mean of HR on the short-term scale changes little, and is almost completely stationary. During anaesthesia in contrast, if HR increases, then 8–45 s later, there is an equal probability of a further HR increase or decrease. Accordingly, the mean of HR can change significantly after a short-term period and can be non-stationary on the short-term scale.

Although we have presented the results of the increased non-stationarity during general anaesthesia on a scale of less than 45 s, the increase also occurs on a greater scale. Figure 3A shows a HR tachogram recorded during sevoflurane anaesthesia. To highlight the non-stationarity for a larger scale of 5 min, we displayed a sequence of average values for the three successive, non-overlapping, 5 min long HR segments in the HR tachogram during the pre-anaesthetic period that is depicted in Figure 3A (c) and the anaesthetic period that is shown in Figure 3B (d). The mean HR continuously decreased during anaesthesia (d) but did not change in the pre-anaesthetic state. However, we could not present the results of increased non-stationarity on larger scales. This is because at the larger scales, the range of scales at which increased non-stationarity occurs differs greatly among patients, and no scale suitable for all patients could be found.

The Hurst exponent quantifies the magnitude of non-stationarity but does not capture the direction (or polarity) of the non-stationarity. Negative polarity and positive polarity indicate progressive bradycardia (Fig. 1A, broken arrows) and progressive tachycardia (Fig. 1B, arrow), respectively. Zero polarity indicates stationarity—no progressive change in mean HR. It could well be that a progressively more prominent bradycardia develops as there is a deepening of depth of anaesthesia in the absence of surgical stimuli. In that case, the non-stationarity is not an indication of stable anaesthesia, but of a deepening of anaesthesia when the steady state is not yet reached. This warrants further study into whether the non-stationarity of HR can be used as a probe for anaesthetic depth or a change in anaesthetic depth. Modification of the algorithm for the Hurst exponent to capture not only the magnitude of the non-stationarity but also the polarity would be needed.

In general, spectral analysis is based on a hypothesis of stationary signal. If the signal is non-stationary, the calculated spectral power contains energy originating not only from oscillation, but also from the non-stationarity. Since HR is highly non-stationary during general anaesthesia, the value of the HR spectral powers during general anaesthesia is influenced by the non-stationarity and by cardiac autonomic nervous activity. Furthermore, during general anaesthesia, autonomic activity is strongly suppressed, and the value is much more influenced by non-stationarity. Accordingly, when evaluating autonomic activity by a power spectral analysis of the HR, simultaneous evaluation of the degree of non-stationarity seems to be mandatory.

![Fig 3](A and B) Two HR tachograms recorded before (A) and during anaesthesia (B) with sevoflurane. (C and D) Plots of the means of the successive non-overlapping 5 min long HR tachograms during the pre-anaesthetic period (C) and the anaesthetic period (D). Note the persistent decrease in the mean HR during the anaesthesia (D).
To identify increased non-stationarity as a phenomenon that occurs universally during general anaesthesia, future studies are needed in adults and to see whether i.v. anaesthetics have similar effects. Furthermore, the magnitude of the parasympathetic modulation of high-frequency oscillation (HFP) in middle-age adults and the autonomic modulation of low frequency oscillation (LFP) in the young adults are significantly smaller and larger, respectively, than in childhood. A future study is also required on whether spectral indices are worse than the short-term Hurst exponent in discriminating between pre-anaesthetic and anaesthetic states in adults.

Spectral analysis shows the difference in cardiac autonomic modulation between sevoflurane and desflurane in children. In adults, desflurane but not sevoflurane can cause neurocirculatory excitation manifest as increased HR, arterial pressure, and sympathetic nerve activity during induction and the transitional period when desflurane concentrations are rapidly increasing. Ebert and Muzzi also showed that during steady-state anaesthesia desflurane results in a progressive increase in sympathetic nerve activity whereas sevoflurane does not. Our study was performed under steady-state sevoflurane or desflurane anaesthesia at 1 MAC concentration, a similar concentration to that used by Ebert. It seems from our study that desflurane-associated sympathetic excitation does not occur in children because the LFP and nLFP during desflurane anaesthesia were not increased but significantly and markedly decreased and because LFP and nLFP during desflurane anaesthesia were not higher than that during sevoflurane anaesthesia. When results of other spectral indices are analysed together, the effect on autonomic modulation between the two anaesthetics in children seems to be different from that in adults. In children, desflurane suppresses autonomic modulation more strongly than sevoflurane does. Unlike sevoflurane, desflurane suppresses parasympathetic modulation more than sympathetic modulation, which is supported by a significant decrease in RRI during the desflurane anaesthetic period (Table 2). We did not further investigate why the sympathetic activation that was observed in the adults during desflurane anaesthesia in Ebert’s study was not observed in the children during desflurane anaesthesia in the current study. However, our result of the spectral analyses showed that the behaviour of the sympathetic nervous system during desflurane anaesthesia in children may be different from that in adults.

In this study, ventilatory rate was set according to age. Different rates may influence HRV, especially the HFP which is affected by respiratory-related vagal HR modulation. HFP values vary with tidal volume and RR, if RR is equal to or less than 8 bpm. Since in our study, ventilatory rate remained at 12–24 bpm in both groups, HFP was unaffected by ventilatory rate.

Non-stationarity markedly increased, despite the strong suppression of autonomic nerve activity by general anaesthesia. Thus, the non-stationarity may be related to the non-neural modulation of HR which may be due to stress hormones, including circulating catecholamines and cortisol, both of which are known to increase during sevoflurane anaesthesia. With marked suppression of the neural modulation of the HR, the non-neural modulation by stress hormones can dominate HR regulation and produce a markedly increased non-stationarity during the anaesthetic period.

If non-stationarity is related to non-neural HR regulation, both spectral and non-stationarity analysis will provide information about both neural and non-neural regulation of HR. Even if future studies fail to prove the relationship between non-stationarity and stress hormones, the short-term non-stationarity exponent provides another way of characterizing HRV in children during general anaesthesia. Future studies should therefore address the question of whether non-stationarity or spectral indices measured during general anaesthesia in children can be used to assess anaesthetic depth or to predict post-anaesthetic outcomes such as cardiovascular instability.

In conclusion, there is a significant increase in HR non-stationarity during sevoflurane or desflurane anaesthesia in children on the short- and very-short-term scales. The increase in short-term non-stationarity is more prominent than the decrease in HR oscillation. We suggest that short-term non-stationarity should be evaluated when characterizing HRV during sevoflurane or desflurane anaesthesia in children.

**Funding**

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